OCT 27 2006
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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jef DE BRABANDER, et al.

Title: ***SYNTHESIS OF PELORUSIDE A AND ANALOGS THEREOF FOR USE AS ANTITUMOR AGENTS***

Appl. No.: 10/783,848 Filing Date: 2/20/2004

Examiner: A. Owens Art Unit: 1625

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

I, Jef De Brabander, hereby declare that:

1. I am an Associate Professor in the Department of Biochemistry at The University of Texas Southwestern Medical Center at Dallas, for the Board of Regents, The University of Texas System, which is the assignee of the captioned application.

2. I conduct research in the fields of chemical synthesis and biological evaluation of biologically active compounds. My qualifications are set out in my *curriculum vitae*, which is attached hereto as APPENDIX A.

3. I am named as an inventor in the captioned application. I also have read and believe that I have understood both an office action, dated June 28, 2006, which concerns the application, and certain documents cited in the action, namely, U.S. Patent Application Publication No. 2002/0193423 to Northcote *et al.* ("Northcote") and L. W. West *et al. J. Org. Chem.* **2000**, *65* 445-449 ("West").

4. Each of the Northcote and West publications describe the isolation from a marine sponge a compound that is designated as peloruside A. In Northcote, peloruside A is identified as having the structure illustrated as Formula III (paragraph 0042). Showing the identical chemical structure, West similarly identifies peloruside A (page 445).

5. Peloruside A is an optically active molecule bearing 10 stereogenic centers; hence, it is one of 2^{10} possible stereoisomers. Both Northcote (paragraph 0027) and West (see abstract) assign the relative stereochemistry for the set of 10 stereogenic centers. While such assignment limits the number of possible stereoisomers to two non-superimposable mirror image structures, neither publication establishes the absolute

stereochemical configuration at each center. Accordingly, Northcote and West do not correctly establish which stereoisomer in fact is peloruside A. Not knowing therefore which of the two possible mirror-imaged structures represents the natural isolated peloruside A, Northcote or West arbitrarily depicted one of the two possible structures in both publications as that of the structure of peloruside A.

6. Informed by either or both of Northcote and West, therefore, the knowledgeable reader would have had no way to discern or to predict (A) whether both possible mirror-imaged stereoisomers are biologically active or whether just one is active and, if the latter instance pertained, (B) which one of the two is the active stereoisomer.

7. As demonstrated in this patent application (No. 10/783,848, paragraph 0186), this arbitrarily depicted structure in the Northcote and West publications is biologically inactive. Confronted with this fact, a knowledgeable reader of either Northcote or West would have had no recourse other than empirical experimentation, unguided by predictive principle or *a priori* expectation of success, in attempting to formulate a pharmaceutical composition pursuant to Northcote's suggestion (see paragraph 0021).

8. Finally, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Respectfully submitted,

Date October 16, 2006 By _____

Jef De Brabander

APPENDIX A

CURRICULUM VITAE

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Education

December 1993	**Ph.D. in Chemistry** (Highest Honors), University of Gent, Belgium
July 1987	**B.Sc. in Chemistry** (Distinction), University of Gent, Belgium

Professional Experience

2005-	**Co-Director** (with Steven L. McKnight), Chemistry and Cancer Scientific Program of the Simmons Comprehensive Cancer Center (directed by Dr. James Willson, M.D.)
2004-	**Chair**, Chemistry Track of the Biological Chemistry Graduate Program
2003-	**Associate Professor** (Department of Biochemistry, UT Southwestern Med Ctr)
1998-2003	**Assistant Professor** (Department of Biochemistry, UT Southwestern Med Ctr)
1996-1998	**Maître d' Assistant** (Instructor) Department of Organic Chemistry, University of Geneva, Switzerland
1995-1996	**Postdoc** (Stanford University; Prof. P. A. Wender)
1994-1995	**Postdoc** (University of Geneva, Switserland; Prof. W. Oppolzer)
1993-1994	**Graduate Teaching Assistant** (University of Gent, Belgium)

Awards, Fellowships, Scholarships

- Prix STAS par l'Académie Royale des Sciences, des Lettres et des Beaux-Arts de Belgique (STAS-award from the Royal Academy of Sciences, Letters and Beautiful Arts of Belgium), December 10, 1994.
- Scholarship from the Institute for Scientific Research in Agriculture and Industry (Belgium), 1989-1992.
- Fellowship from the Swiss National Science Foundation, 1994-1995.
- Fulbright-Hays Award, 1995-1996.
- NATO-fellowship, 1995-1996.
- Alfred P. Sloan Research fellowship 2001-2003.
- "Journal Award" from the editorial boards of *Synlett* and *Synthesis,* 2006.
- Academic Development Program Award from the Chemistry Council of Merck Research Laboratories.

Grant Support

- The Robert A. Welch Foundation: "Synthesis of Salicylhalamides A-B and Lobatamides A-F: Novel Macrocyclic Anti-Tumor Compounds with a Unique Differential Cytotoxicity Profile" (06/01/99-05/31/02; $135,000 total direct costs). **COMPLETED**
- NIH R01 CA90349: "Chemistry and Biology of Salicylate Natural Products" (03/01/01-02/28/06; $866,125 total direct costs). **COMPLETED**
- NIH Lung Cancer SPORE (P50 CA70907), Career and Developmental Project Award: "*In Vitro* and *In Vivo* Evaluation of Synthetic Salicylihalamides" (01/01/01-08/31/01; $25,000 total direct costs). **COMPLETED**
- Alfred P. Sloan Research fellowship from September 16, 2001 – September 15, 2003 ($40,000 total direct costs). **COMPLETED**
- Texas Higher Education Coordinating Board, Advanced Research program – Chemistry (010019-0040-2001): " Synthesis of Peloruside A" (01/01/02-12/31/03; $131,424 total direct costs). **COMPLETED**
- NIH Program Project Grant (P01CA95471, PI: Steven L. McKnight; Co-PI on projects 1 and 2): "A Concerted Chemical, Biophysical and Molecular Biological Attack of Intracellular Pathways Relevant to Human Cancer" [09/01/02-08/31/07: $11,191,307 total direct costs. **ACTIVE**

- The Robert A. Welch Foundation: "Evaluation of Cyclohexadienone Photochemistry for the Assembly of Macrocyclic Natural Product-Like Compounds" (06/01/02-05/31/05; $155,000 total direct costs). **COMPLETED**
- Merck Research Laboratories: Unrestricted Research Grant (October 2004 – October 2005, $25,000 direct costs). **COMPLETED**
- The Robert A. Welch Foundation: "Synthetic Studies Toward Spirastrellolide" (06/01/05-05/31/08; $180,000 total direct costs). **ACTIVE**
- Merck Research Laboratories: Unrestricted Research Grant (October 2005 – October 2006, $25,000 direct costs). **COMPLETED**
- NIH R01 CA90349: "Chemistry and Biology of Antitumor Natural Products" (03/01/06-02/28/11; $828,100 total direct costs). **ACTIVE**

Publications

- De Brabander B, D'haeseleer F, De Brabander M, Distelmans W, Van Ginckel R, De Brabander J (1989) The Protective Effect of Behavioral Activation on the Growth of a Syngeneic Tumor and Mortality in Socially Stressed Mice. *European Journal of Psychiatry* 3, 238-244.
- De Brabander J (1989) Chimie Organometallique: La Chimie des Métaux de Transition; Applications dans la Synthèse Organique. *Chimie Magazine* (Belgium) 15, 23.
- De Brabander J, Vanhessche K, Vandewalle M (1991) Bryostatins: The Asymmetric Synthesis of C1-C9 and C11-C16 Fragments. *Tetrahedron Letters* 32, 2821.
- De Brabander J, Vandewalle M (1994) Bryostatins: The Asymmetric Synthesis of the C17-C27 Fragment. *Synlett*, 231.
- De Brabander J, Vandewalle M (1994) Bryostatins: The Asymmetric Synthesis of the C1-C9 and C17-C27 Fragments. *Synthesis*, 855-866 (Feature Article).
- Oppolzer W, Radinov RN, De Brabander J (1995) Total Synthesis of the Macrolide (+)-Aspicilin by an Asymmetrically Catalyzed Macrocyclization of an ω-Alkynal Ester. *Tetrahedron Lett*ers 36, 2607-2610.
 Subject of commentary in 'Nachr. Chem. Tech. Lab. 1996, vol.44, Nr. 2' and 'Chemistry & Industry 1995, June Issue, p.465.'
- Oppolzer W, De Brabander J, Walther E, Bernardinelli G (1995) Asymmetric Synthesis of (–)-Denticulatins A and B *via* Group-Selective Aldolization of a *Meso* Dialdehyde with a Chiral *N*-Propionylsultam. *Tetrahedron Letters* 36, 4413-4416.
 Subject of commentary in 'Chemtracts-Org. Chem. 1996, March/April Issue, p.134' and 'Nachr. Chem. Tech. Lab. 1996, vol.44, Nr. 6, p.612.'
- De Brabander J, Vandewalle M (1996) Towards the Asymmetric Synthesis of Bryostatin 1. *Pure and Applied Chemistry* 68, 715-718.
- Oppolzer W, Walther E, Balado CP, De Brabander J (1997) Enantioselective Synthesis of the Prelog-Djerassi Lactonic Acid *via* Group-Selective Aldolization/Desymmetrization of a *Meso* Dialdehyde with a chiral *N*-Propionylsultam. *Tetrahedron Letters* 38, 809-812.
- Oppolzer W, Rosset S, De Brabander J (1997) Asymmetric Synthesis of Ibuprofen *via* Diastereoselective Alkylation of a Homochiral *N*-Acyl Bornanesultam. *Tetrahedron Letters* 38, 1539-1540.
- De Brabander J, Kulkarni BA, Garcia-Lopez R, Vandewalle M (1997) Bryostatin: A Novel Asymmetric Synthesis of the C_{27}-C_{34} Fragment Starting from (*R*)-Carvone as Chiral Template. *Tetrahedron Asymmetry* 8, 1721-1724.
- De Brabander J, Rosset S, Bernardinelli G (1997) Towards a Synthesis of Epothilone A: Rapid Assembly of the C1-C6 and C7-C12 Fragments. *Synlett*, 824-826.
- Oppolzer W, Darcel C, Rochet P, Rosset S, De Brabander J (1997) Non-Destructive Removal of the Bornanesultam Auxiliary in α-substituted *N*-Acylbornane-10,2-sultams Under Mild Conditions: An Efficient Synthesis of Enantiomerically Pure Ketones and Aldehydes. *Helvetica Chimica Acta* 80, 1319-1337.
- De Brabander J, Oppolzer W (1997) Enantioselective Total Synthesis of (-)-Denticulatins A and B Using a Novel Group-Selective Aldolization of a *Meso* Dialdehyde as a Key Step. *Tetrahedron* 53, 9169-9202.
- De Brabander J, Kulkarni BA, Garcia-Lopez R, Vandewalle M (1997) (*R*)-Carvone as Chiral Template for the Synthesis of Some Polyols. *Bull. Soc. Chim. Belg., European Section* 106, 665-669.
- Wender PA, De Brabander J, Harran PG, Jimenez JM, Koehler MFT, Lippa B, Park CM (1998) Synthesis of the First Members of a New Class of Biologically Active Bryostatin Analogs. *Journal of the American Chemical Society* 120, 4534-4535.

Subject of commentary in 'Chemistry & Engineering News 1998, May 18 Issue, p.35' and 'Chemistry & Engineering News 1999, September 20 Issue, p.70'

- Wender PA, De Brabander J, Harran PG, Jimenez JM, Koehler MFT, Lippa B, Park CM, Siedenbiedel C, Pettit GR (1998) The Design, Computational Analysis, Solution Structure and Biological Evaluation of the First Totally Synthetic Analogs of Bryostatin. *Proceedings of the National Academy of Sciences USA* 95, 6624-6629.
 Subject of commentary in 'Chemistry & Engineering News 1999, September 20 Issue, p.70'
- Wender PA, Martin-Cantalejo Y, Carpenter AJ, Chiu A, De Brabander J, Harran PG, Jimenez JM, Koehler MFT, Lippa B, Morrison JA, Müller SG, Müller SN, Park CM, Shiozaki M, Siedenbiedel C, Skalitzky DJ, Tanaka M, Irie K (1998) The Chemistry-Medicine Continuum: Synthetic, Computer, Spectroscopic, and Biological Studies on New Chemotherapeutic Leads. *Pure & Applied Chemistry* 70, 539.
- Wender PA, De Brabander J, Harran PG, Hinkle KW, Lippa B, Pettit GR (1998) Synthesis and Biological Evaluation of Fully Synthetic Bryostatin Analogues. *Tetrahedron Letters* 39, 8625-8628.
- Wu Y, Esser L, De Brabander JK (2000) Revision of the Absolute Configuration of Salicylihalamide A through Asymmetric Total Synthesis. *Angewandte Chemie International Edition* 39, 4308-4310.
 Subject of a television broadcast by the Dallas/Fort-Worth CBS news-station (Health Alert) on the evening news, December 7th, 2000 and a nationwide radio broadcast by the American Association for the Advancement of Science.
- Bhattacharjee A, De Brabander JK (2000) Synthesis of Side Chain Truncated Apicularen A. *Tetrahedron Letters* 41, 8069-8073.
- Wu Y, Seguil OR, De Brabander JK (2000) Synthesis and Initial Structure-Activity Relationships of Modified Salicylihalamides. *Org. Lett.*, 2, 4241-4244.
- Randle DE, Wu Y, De Brabander J, Minna J (2001) In vitro characterization of salicylihalamides: A new class of anticancer drugs. *Clinical Cancer Research* 7 (11), 473 Suppl. S.
- Bhattacharjee A, Seguil OR, De Brabander JK (2001) Total synthesis and biological evaluation of apicularen A and synthetic analogs. *Tetrahedron Letters* 42, 1217-1220.
- Bhattacharjee A, Soltani O, De Brabander JK (2002) Synthesis of the C1-C21 (C1'-C21') Fragment of the Dimeric Polyketide Natural Product SCH 351448. *Organic Letters* 4, 481-484.
- Esser L, De Brabander JK (2002) 2-[(7*R*,9*S*,10*R*,12*E*)-4,9-Dihydroxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro-5*H*-6-oxa-benzocyclododecen-7-yl]ethyl octanoate. *Acta Crystallographica* E58, o142-o144.
- Wu Y, Liao X, Wang R, Xie X-S, De Brabander JK (2002) Total Synthesis and Initial Structure–Function Analysis of the potent V-ATPase Inhibitors Salicylihalamide A and Related Compounds. *Journal of the American Chemical Society* 124, 3245-3253.
- Liao X, Wu Y, De Brabander JK (2003) Total Synthesis and Absolute Configuration of the Novel Microtubule Stabilizing Agent Peloruside A. *Angewandte Chemie International Edition* 42, 1648-1652.
 Subject of commentary in 'Chemistry & Engineering News 2003, April 14 Issue, p.35'
- Xie X-S, Padron-Perez D, Liao X, Wang J, Roth MG, De Brabander JK (2004) Salicylihalamide A inhibits the V_0 sector of the V-ATPase through a mechanism distinct from bafilomycin A_1. *Journal of Biological Chemistry* 279, 19755-19763 (published online, March 3, 2003).
- Li L, Thomas RM, Suzuki H, De Brabander JK, Wang X, Harran PG (2004) A small molecule Smac Mimic poptentiates TRAIL and TNFα mediated cell death. *Science* 305, 1471-1474.
 Subject of commentary in 'Science (Perspectives) 2004, 305, p.1411-1413' and 'Chemistry & Engineering News 2004, September 6 Issue, p.35'
- Lebreton S, Xie X-S, Ferguson D., De Brabander JK (2004) Ring-closing metathesis: A powerful tool for the synthesis of simplified salicylihalamide-based V-ATPase inhibitors. *Tetrahedron* 60, 9635-9647.
- Adams CM, Reitz J, De Brabander JK, Feramisco JD, Li L, Brown MS, Goldstein JL (2004) Cholesterol and 25-Hydroxycholesterol Inhibit Activation of SREBPs by Different Mechanisms, Both Involving SCAP and Insigs. *Journal of Biological Chemistry* 279, 52772-52780 (published online, September 27, 2004).
- Soltani O, De Brabander JK (2005) Synthesis of Functionalized Salicylate Esters and Amides via Photochemical Acylation. *Angewandte Chemie International Edition* 44, 1696-1699.
- García-Fortanet J, DeBergh JR, De Brabander JK (2005) A photochemical Entry to Depsides: Synthesis of Gustastatin. *Organic Letters* 7, 685-688.
- Soltani O, De Brabander JK (2005) A Concise Synthesis of (+)-SCH 351448. *Organic Letters* 7, 2791-2793.
- Jiang X, García-Fortanet J, De Brabander JK (2005) Synthesis and Complete Stereochemical Assignment of Psymberin / Irciniastatin A. *Journal of the American Chemical Society* 127, 11254-11255.

- Pan Y, De Brabander JK (2006) Synthesis of Spirastrellolide A Fragments for Structure Elucidation. *Synlett*, 853-856.
- Liu B, De Brabander JK (2006) Metal-Catalyzed Regioselective Oxy-Functionalization of Internal Alkynes: An Entry into Ketones, Acetals, and Spiroketals. *Organic Letters* 8, 4907-4910.
- Jiang X, Williams N, De Brabander JK "Synthesis of Psymberin Analogs: Probing a Functional Correlation with the Pederin/Mycalamide Family of Natural Products", submitted to *Organic Letters*.
- Jiang X, De Brabander JK "Total Synthesis of the Antarctic Marine Metabolite (–)–Palmerolide A", in preparation.

Patents

- De Brabander JK, Wu Y "Synthetic Salicylihalamides, Apicularens and Derivatives Thereof", Patent Application filed to the United States Patent and Trademark Office (August 3, 2001); Serial No. 09/922,372 (US patent issued 09/09/03; No: 6617348)
- De Brabander JK, Liao X "Synthesis of Peloruside A and Analogs Thereof For Use as Antitumor Agents", Patent Application filed to the United States Patent and Trademark Office (February 20, 2004); Serial No. 10/783,848.
- Harran PG, Wang X, De Brabander JK, Li L, Thomas RM, Suzuki H "Dimeric Small Molecule Potentiators of Apoptosis", Patent Application filed to the United States Patent and Trademark Office (March 1, 2004); serial No. 60/549,520.
- De Brabander JK, Jiang X "Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin for use as Antitumor Compounds", Patent Application filed to the United States Patent and Trademark Office (July 15, 2005); serial No. 11/182,069.

Invited Lectures at Major National and International Conferences

- Gordon Research Conference on Natural Products Chemistry, Plymouth State College, NH, July 30-August 4, 2000.
- 222nd American Chemical Society National Meeting (Organic Chemistry Division, Abstract ORGN-161), Chicago, IL, August 26-30, 2001.
- National Science Foundation Workshop on Organic Synthesis, Colorado Mountain Lake Resort, Ward, CO, July 12-16, 2001.
- Gordon Research Conference on Natural Products Chemistry, Tilton School, Tilton, NH, July 2004.
- American Chemical Society National Meeting ("Diversity-Oriented Synthesis and Chemogenomic Drug Discovery" symposium), Philadelphia, PA, August 22-26, 2004.
- Keynote speaker at SICC-4 (Singapore International Chemical Conference), December 8-10 2005, Shangri-La Hotel, Singapore.
- ManaproXII (Marine Natural Products), February 4-7 2007, Queenstown, New Zealand.
- 20th International Symposium in Organic Chemistry, July 16-19 2007, Churchill College, Cambridge, UK.
- 10th International Conference on the Chemistry of Antibiotics and other Bioactive Compounds (ICCA-10), August 12-15 2007, Vanderbilt University, Nashville, TN.
- Gordon Research Conference on Natural Products Chemistry, Tilton School, Tilton, NH, July 2008.

Other Invited Lectures (Universities, Industry, etc.)

- Meeting Organic Synthesis (DSM-Research), Kasteel Vaalsbroek, Holland, March 29-31, 1993.
- University of Gent, Belgium, December 1994.
- Workshop Swiss National Science Foundation-Division of Science and Engineering, Gwatt, Switzerland, March 29-30, 1995.
- Autumn meeting 1995, New Swiss Chemical Society, Bern, Switzerland, October 1995 (*Chimia* **1995**, *49*, 259).
- Corporate Research Units, Ciba-Geigy AG, Basel, Switzerland, October 11, 1995.
- BASF, Frankfurt, Germany, November 24, 1997.
- University of Texas at Dallas, TX, November 10, 1999.
- Southern Methodist University, Dallas, TX , November 16, 1999.
- University of Geneva, Geneva, Switzerland, October 5, 2000.
- Serono Pharmaceutical Research Institute, Geneva, Switzerland, October 9, 2000.
- Alcon Universal LTD., Fort Worth, TX, November 10, 2000.
- Vrije Universiteit Amsterdam, Amsterdam, March 9, 2001.

- Washington University, St. Louis, MO, March 21, 2002.
- University of North Carolina, Chapel Hill, NC, April 12, 2002.
- UT Southwestern Medical Center, Biochemistry Department, Dallas, TX, April 18, 2002.
- Bristol-Myers Squibb, Lawrenceville campus, NJ, April 23, 2002.
- UT Southwestern Medical Center, Medical Scientists Training Program, Dallas, TX, May 7, 2002.
- Columbia University, New York, NY, May 9, 2002.
- Abbott Laboratories, June 7, 2002.
- Ely Lilly, Indianapolis, Indiana, June 18, 2002.
- Vanderbilt University, Nashville, TN, September 23, 2002.
- Merck, February 21, 2003.
- Texas A&M University, College Station, TX, March 6, 2003.
- SCRIPPS, La Jolla, CA, April 22, 2003.
- UC Irvine, Irvine, CA, April 23, 2003.
- UC Berkeley, Berkeley, CA, September 16, 2003.
- Abbott Laboratories Seminar Series, University of Notre Dame, Notre Dame, IN, April 14, 2004.
- Victoria University of Wellington, Wellington, New Zealand, May 25, 2004.
- Merck Research Laboratories, West Point, PA, June 11, 2004.
- Johnson & Johnson, New Jersey, September 28, 2004.
- Trinity University, San Antonio, TX, October 28, 2004.
- Bristol-Myers-Squibb Lecturer, UT Austin, Austin, TX, October 29, 2004.
- University of California Santa Barbara, April 14, 2005.
- Amgen, Thousand Oaks, California, April 15, 2005.
- Case Western Reserve University, Ohio, September 1, 2005.
- UT Galveston, Galveston, TX, October 7, 2005.
- North Caroline State University, Raleigh, NC, November 21, 2005.
- Southwestern *In Vivo* Cancer Cellular and Molecular Imaging Program, UT Southwestern Medical Center, Dallas, TX, November 30, 2005.
- Pharmacology Seminar Series, UT Southwestern Medical Center, Dallas, TX, January 12, 2006.
- UC Santa Cruz, Santa Cruz, California, January 30, 2006.
- UT Arlington, Arlington, Texas, April 7, 2006.
- Roche, Palo Alto, CA, April 13, 2006.
- Yale University, New Haven, CT, November 1, 2006.
- University of Pittsburgh, Pittsburgh, PA, March 1, 2007.

Selected Professional Activities

- Reviewer for the following international scientific journals: Journal of the American Chemical Society, Organic Letters, Angewandte Chemie International Edition, Tetrahedron Letters, Tetrahedron, Chemistry – A European Journal, Journal of Organic Chemistry, Synlett, ChemBioChem, Bioorganic and Medicinal Chemistry Letters, Canadian Journal of Chemistry
- *Ad Hoc* reviewer for the National Science Foundation
- Reviewer for the National Institutes of Health Study Sections.
- Founding Member and Member of the Scientific Advisory Board of Reata Pharmaceuticals, Inc.

Professional Affiliations

American Chemical Society; American Association for the Advancement of Science